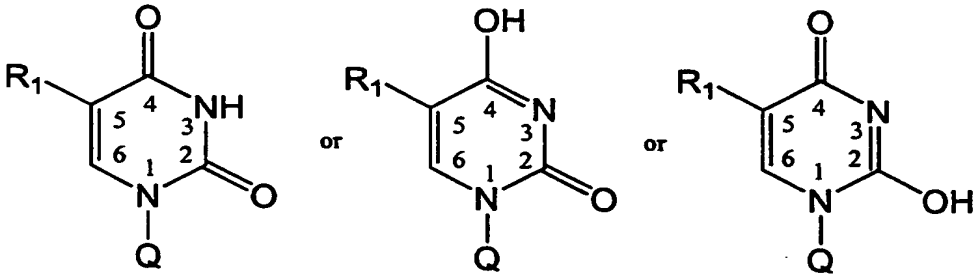
CLAIMS

What is claimed is:

1. A method for selectively inhibiting the proliferation an infectious agent, wherein the infectious expresses an activating enzyme and wherein the activating enzyme is not inactivated by a substrate prodrug compound, the method comprising contacting the infectious agent or a cell infected with the agent with an effective amount of the substrate compound that is selectively converted to a toxin by the activating enzyme, thereby selectively inhibiting the proliferation of the infectious agent.

2. The method of claim 1, wherein the substrate prodrug is an L or D compound of the structure:

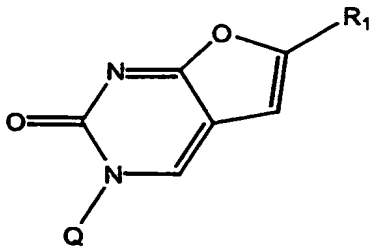
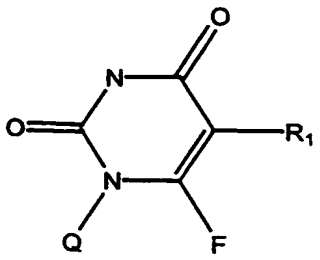
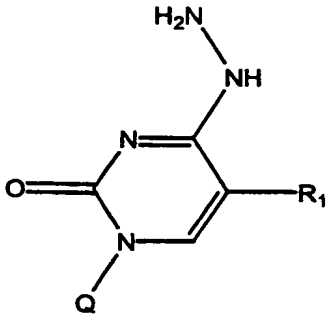


wherein R_1 is or contains a leaving group which is a chemical entity that has a molecular dimension and electrophilicity compatible with extraction from the pyrimidine ring by the activating enzyme, and which upon release from the pyrimidine ring by the activating enzyme, has the ability to inhibit the proliferation of the agent or the cell; and

wherein Q is a moiety selected from the group consisting of a sugar, a carbocylic, an acyclic compound and masked phosphate or phosphoramidate derivatives thereof.

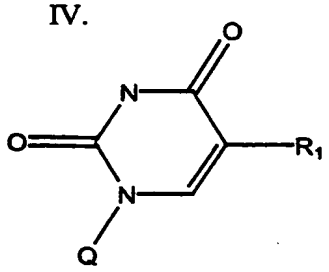
3. The method of claim 1, wherein the compound has the structure:

I. or II. or III.

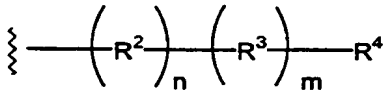
or

IV.



wherein:

R^1 is a moiety of the formula:



with the proviso that in compound I, n can be 0.

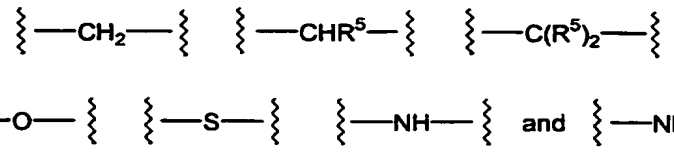
R^2 is a divalent electron conduit moiety selected from the group consisting of:

an unsaturated hydrocarbyl group;

an aromatic hydrocarbyl group comprising one or more unsaturated hydrocarbyl groups; and,

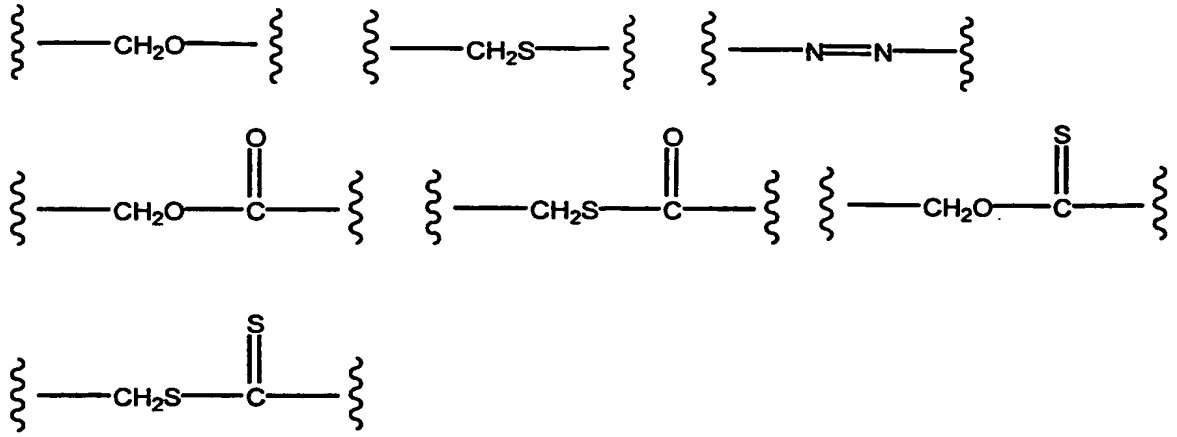
a heteroaromatic group comprising one or more unsaturated hydrocarbyl groups;

R^3 is a divalent spacer moiety selected from the group consisting of:



and

;

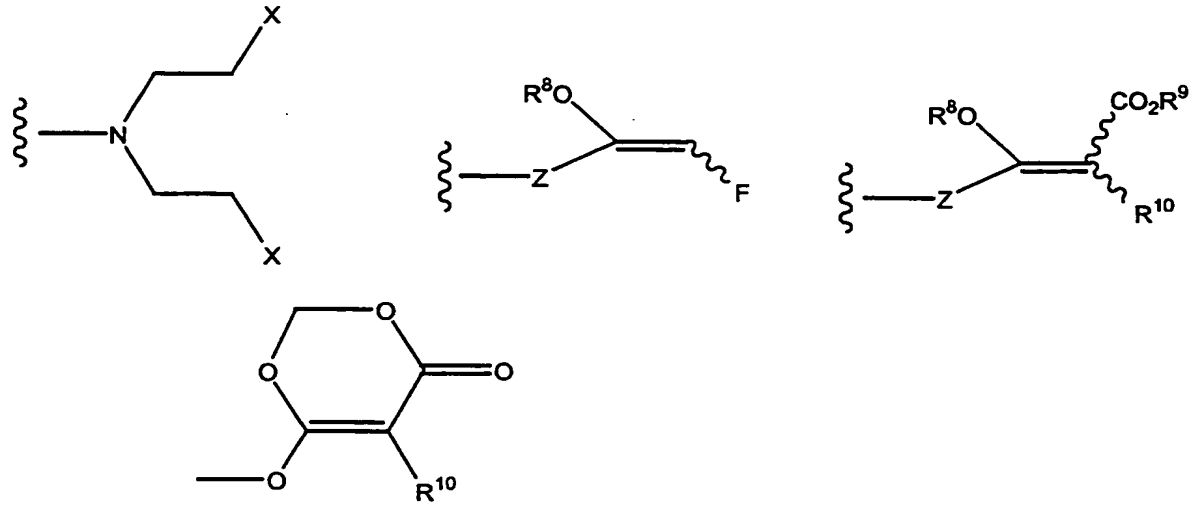


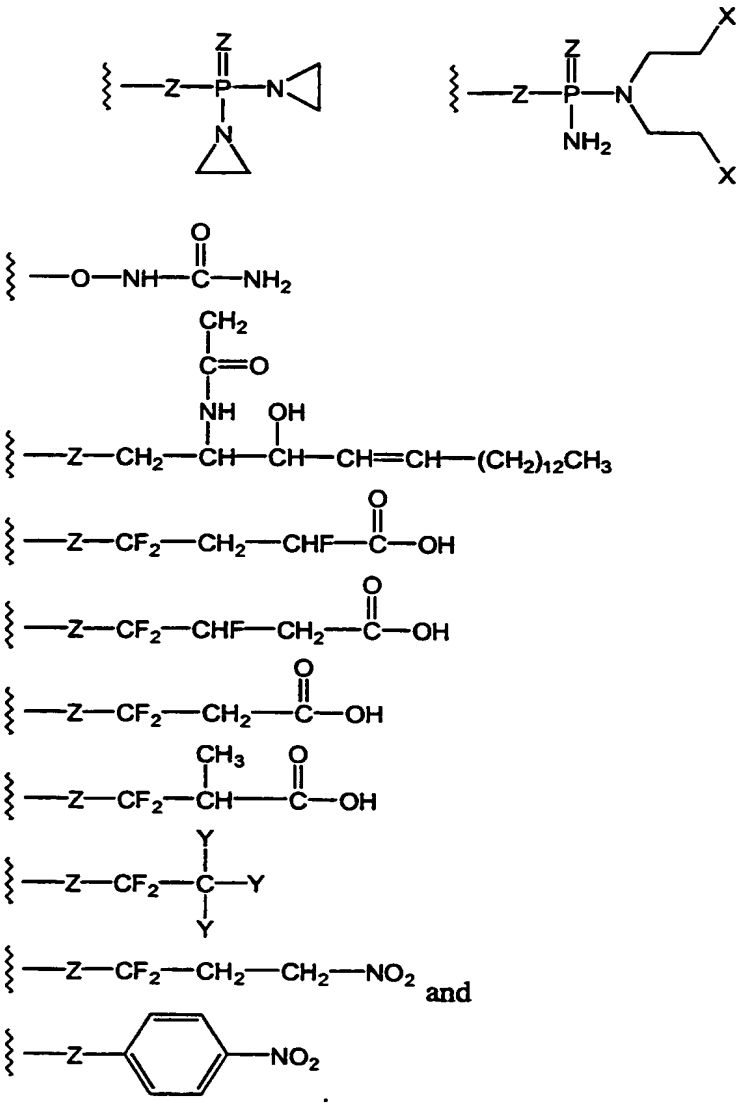
R^5 may be the same or different and is independently a linear or branched alkyl group having from 1 to 10 carbon atoms, or a cycloalkyl group having from 3 to 10 carbon atoms, or a halogen (F, Cl, Br, I);

n is an integer from 0 to 10;

m is 0 or 1;

R^4 is a toxophore moiety selected from the group consisting of:





and

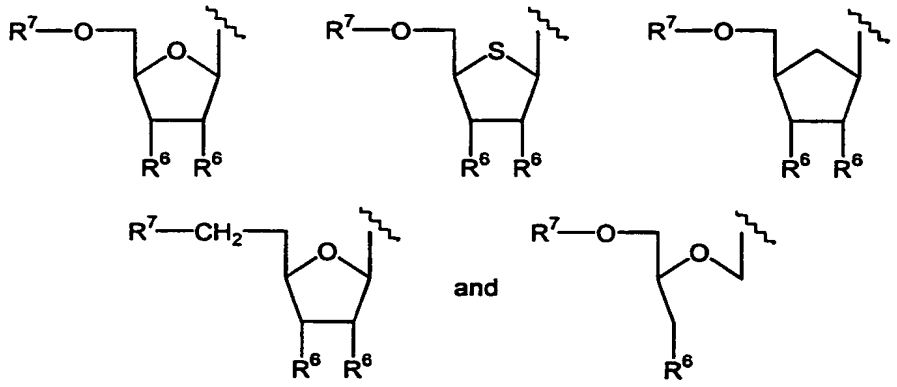
R^8 and R^9 are lower alkyls and R^{10} is H or CH_3

X is -Cl, -Br, -I, or other potent leaving group, with the proviso that when R^7 is -H, and m is zero, then R^4 is not a halogen or when m is zero and n is zero, then R^4 is not a halogen;

Y is independently -H or -F;

Z is independently -O- or -S-;

Q is a moiety selected from the group consisting of:



R^6 is independently -H, -OH, $-OC(=O)CH_3$, F, or other protected hydroxyl group; and,

R^7 is hydrogen, a phosphate group, a phosphodiester group, or a phosphoramidate group;

and wherein said compound may be in any enantiomeric, diasteriomeric, or stereoisomeric form, including, D-form, L-form, α-anomeric form, and β-anomeric form.

4. The method of claim 1, wherein the infectious agent is selected from the group consisting of a bacteria, a parasite, a virus, and a yeast.

5. The method of any of claims 1 to 4, wherein the activating enzyme is thymidylate synthase.

6. The method of any of claims 1 to 4, wherein the activating enzyme is selected from the group consisting of thymidylate synthase, beta-lactamase, viral proteases, dihydrofolate reductase or viral reverse transcriptase.

7. The method of any of claims 1 to 4, wherein the contacting is *in vitro*, *ex vivo* or *in vivo*.

8. The method of claim 1, wherein the contacting is *in vivo*.

9. The method of any of claims 1 to 4, further comprising contacting the agent or the cell with an effective amount of a second agent that inhibits proliferation of the infectious agent.

10. A method for screening for prodrugs selectively converted to a toxin by an activating enzyme expressed by an infectious agent, wherein the prodrug is not inactivated by the prodrug, comprising contacting a candidate prodrug with the infectious agent or a cell

infected with the infectious agent that expresses the activating enzyme and assaying for inhibition of proliferation of the infectious agent or the cell infected by the infectious agent.

11. The method of claim 10, further comprising contacting a normal, unifected cell with the candidate prodrug and assaying for inhibition of growth or proliferation fo the normal cell by the candidate prodrug.

12. The method of claim 10, wherein the activating enzyme is thymidylate synthase expressed by the infectious agent.

13. The method of any of claims 1 to 4, wherein the activating enzyme is selected from the group consisting of thymidylate synthase, beta-lactamase, viral proteases, dihydrofolate reductase or viral reverse transcriptase.

14. The method of any of claims claims 10 to 13, wherein the assay comprises analysis of intracellular metabolites of the candidate prodrug by mass spectrometry.

15. The method of any of claims 10 to 13, wherein the candidate agent comprises a detectable agent.

16. The method of claim 15, wherein the detectable agent is a fluorescent marker.

17. The method of claims 1 or 10, wherein the activating enzyme is wild-type enzyme.

18. The method of claims 1 or 10, wherein the activating enzyme is a mutated version of the enzyme.

19. The method of claim 18, wherein the activating enzyme is a mutated version that is resistant to a therapy.

20. The method of claim 18, wherein the activating enzyme is a mutated version of HIV-1 reverse transcriptase that exhibits resistant to 3'-axido-3'-deoxythymidine (AZT).